was observed in mice receiving a single dose of silica (3mg silica/mouse IV) one day prior to GVHD induction as compared to mice receiving Tcon only (77 days vs. 29 days, respectively, P = 0.0164). This result correlated with a decrease in Tcon proliferation as illustrated by whole body bioluminescence imaging (BLI) as well as *ex vivo* imaging of lymph nodes, spleen and gastrointestinal tract. This decrease in T con proliferation was confirmed with CFSE-labeled Tcon re-isolated on day 5 after BMT, with 50% of CD4+ T cells proliferated in the pLN of control mice, yet only 30% proliferated in silica treated mice (30%, P = 0.0004). The spleen showed more proliferation of CD4+ T cells overall, however there was still a significantly less proliferation in mice receiving silica than in control mice (79% and 95%, respectively, P = 0.0023). In addition, silica treatment resulted in less overall inflammation as indicated by analysis of serum cytokine levels. In particular, significantly less IFNγ, TNF-α, IL-2, IL-4, IL-5, GM-CSF, IL-10, and IL-12 were detected in the serum from mice treated with silica than from control mice. Together, these results suggest that silica-induced impairment of macrophage function results in reduced T con proliferation, reduced inflammation, and prolonged survival after GVHD induction.

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OPTIMIZATION OF ANTI-THYMOCYTE GLOBULIN EXPOSURE IN PAEDIATRIC BONE MARROW TRANSPLANTATION IN ORDER TO DESIGN AN INDIVIDUALIZED DOSING REGIMEN

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Background: Hematopoietic stem cell transplantation (HSCT) is complicated by severe infectious complications during the lymphopenic period after HSCT, which increases mortality and morbidity. Anti-thymocyte globuline (ATG) is administered prior to allogeneic HSCT to reduce risks of graft-rejection and graft versus host (GvHD). Large interpatient variations in pharmacokinetics (PK) of ATG have been reported, possibly due to differences in bodysize, cell numbers prior to ATG, "the given graft", and other patient characteristics.

Currently, all patients receive the same dose based on bodyweight. This non-individualized dosage is likely to either increases the risk of GvHD (by under dosing) or delays post-tranplant immune reconstitution (by overdosing). This study aims to explain the relation between the above mentioned patient and HSCT related characteristics and the pharmacokinetics of ATG as a basis to design an individualized dosing regimen.

Methods: 142 patients, ranging between 4.5 and 80 kg body weight, who received HSCT between 2004 and 2009 in the two Dutch pediatric hospitals were included. 72 patients received bone marrow, 48 cord blood and 22 peripheral stem cell transplants, containing 2^3 to 1^{10} CD34+cells. A median dose of rabbit ATG (Imtix) of 10mg/kg was given in consecutive 4 days. The level of active ATG capable of binding to T lymphocytes (HUT 78) was measured by quantitative flow cytometry (FACS), total ATG by ELISA. PK analysis was performed using NONMEM.

Results: Large interindividual variability was observed in PK of ATG. Preliminary results of the pharmacokinetic model of active ATG showed a linear relationship between body weight and clearance in children under approximately 20 kg body weight. In children over 20 kg large variability was observed, which could not be explained by bodyweight. In 15 Patients, who produced IGG-antibodies against ATG a more rapid clearance was observed in comparison with patients who did not form antibodies.

Conclusions: The results of the pharmacokinetic model show that a fixed dose of 10 mg/kg in all pediatric patients does not lead to the same exposure of active ATG in all patients ranging 1 month and 21 years of age. Optimization of the pharmacokinetic will be performed in order to derive a paradigm for individualized dosing, leading to a more predictable exposure in all patients.

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INCIDENCE AND OUTCOME OF ADENOVIRUS INFECTION IN ADULT ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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Background: True adenovirus infection, but has been reported in 5-20% of allogeneic hematopoietic stem cell transplant (allo HCT) recipients, with < 2% of patients developing severe adenoviral disease. Adenovirus infection is generally associated with profound immunosuppression and a poor outcome. We evaluated the incidence and significance of adenovirus detection among allo HCT recipients at our institution between 1999 and 2009.

Methods: Viral culture was used to isolate adenovirus from various sterile and non-sterile sources. An immunofluorescence assay was used for confirmation. Definitive infection was the isolation of adenovirus from a sterile source with tissue invasion and compatible clinical presentation. Probable infection represented isolation of the virus from a non-sterile source without tissue data but with compatible clinical features. Disseminated disease was defined as the involvement of > 2 organs.

Results: Seventy-five patients with at least one positive adenovirus culture, representing 1.4% of all allo HCT recipients during the study period, were identified. Transplant types were matched related (36; 48%), matched unrelated (22; 29%), haploidentical (9; 12%), and umbilical cord blood (8; 10%). At the time of adenovirus infection, acute (gradeII-IV) or chronic graft versus host disease (GVHD) was present in 18 (24%) and 30 patients (40%), respectively. Sixty-nine of these patients had probable adenovirus infection while 6 had definitive infection. Thirteen patients (17%) had disseminated disease. Median time from allo HCT to adenovirus infection was 4.8 months (range 0.3 to 80). Eight patients (10%) received anti-adenovirus treatment with cidofovir. The most common clinical manifestations were pneumonia (20, 27%), hemorrhagic cystitis (13, 17%), upper respiratory tract infections (12, 16%), and enteritis (11, 15%). Median overall survival was 5 months and the 2-year survival was 33%. The presence of acute GVHD (p = 0.001), treatment with methylprednisolone (p = 0.0003) and disseminated adenovirus disease (p = 0.02) were associated with a significantly shorter overall survival. In contrast, the type of allo HCT, use of cidofovir, ATG, or probable vs. definitive adenovirus infection did not have a significant impact on survival.

Conclusions: Adenovirus infection is relatively uncommon after allo HCT. Dissemination of adenovirus is associated with a significantly poor outcome in patients with acute GVHD and systemic use of steroids.

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KL-6 AS A MARKER FOR BRONCHIOLITIS OBLITERANS IN PEDIATRIC AND YOUNG ADULT BONE MARROW TRANSPLANT PATIENTS

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Background: Bronchiolitis obliterans syndrome (BOS) is a serious complication of allogeneic bone marrow transplant (BMT). There is a need for a non-invasive diagnostic test in order to detect BOS in transplant recipients. KL-6 is a high molecular weight glycoprotein classified as MUC1 mucin that is expressed on the epithelial surface of type II alveolar cells in the lungs and is present on the surface of bronchiolar epithelial cells. KL-6 is an active chemotactic factor for fibroblasts which could play a role in the early pathogenesis of BOS.

Objective: We hypothesize that serum KL-6 levels will be elevated in subjects with known BOS.

Study Design: This is a case control study that employs convenience sampling for KL-6 samples. It is a multi-center study.

Methods: Serum samples were obtained from 15 subjects that underwent allogeneic BMT and 20 healthy controls between the ages of 6 months and 30 years. Of the 15 subjects that underwent BMT, 3 met the criteria for BOS. The definition of BOS was based upon pulmonary function tests (a sustained drop in FEV1 of 20% from pre-transplantation baseline) or biopsy. KL-6 levels were